PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and risk factors of latent tuberculosis infection in Africa: A systematic review and meta-analysis protocol
AUTHORS	Basera, Tariro; Ncayiyana, Jabulani; Engel, Mark

VERSION 1 - REVIEW

REVIEWER	Neil Schluger Columbia University, USA
REVIEW RETURNED	20-Jun-2016

GENERAL COMMENTS	I think the plans for the review are solid throughout, though I do not understand why the authors will omit studies which used IGRA to determine LTBI prevalence. There are data to support the idea that IGRA are more sensitive in immunocompromised hosts, and this could be highly relevant in places where there is a high prevalence of HIV infection. The increased specificity of IGRA as compared to TST is also a potential advantage. At any rate, I do not think it makes sense to exclude these studies uniformly. I would favor including them if they meet the other criteria set forth for inclusion of TST studies.

REVIEWER	Padmanesan Narasimhan Lecturer School of Public Health and Community Medicine The University of New South Wales Sydney Australia NSW 2052
REVIEW RETURNED	28-Jun-2016

GENERAL COMMENTS	The authors want to estimate the prevalence of LTBI in Africa. The methodology sounds appropriate but there are concerns with the inclusion criteria such as region inclusion, tests used, the derivatives from the study and extraction of such data, handling of mixing of information with TST and IGRA etc. I have given detailed comments and I hope the authors can fix this. Page 2 Line 13- What is the strategy to address studies which have calculated LTBI using both TST and IGRA? Line 20- 'Any study design' is too vague, need to be clearer on what type of studies will be included

	Page 3
	Line 5- Here you mention summarise the burden? But the extract states 'to evaluate the burden'. I think the study research question needs to be very clear
	Line 19-26- Not clear what the author wants to state and how is this is a strength and limitation of the study
	Page 4
	Line 10-12- The study referenced Corbett et al only states an estimated 30% of the world population (1.8 billion people) carried MTB in 2000. Please correct this statement
	Line 26-28- Latent TB infection estimates increasing with immunosuppression- If TST has been used in these studies, it is wise to address the limitation of the test in anergic and immunosuppressive population.
	Line 28-30- This doesn't fit well here. May be you can move this to the first few lines
	Lines 40-49- Other risk factors like Age, diabetes, malnutrition etc. should also be mentioned.
	Page 5
	Lines 3-5- How can we screen 1/3 of the world and treat them for LTBI? This statement is very loose, broad with no evidence base and I suggest removing this.
	Page 6
	Lines 3-5 The previous page talks about the lack of good tools for latent TB diagnoses and the research question doesn't gel with the previous section. The case for doing this review is different to what was stated in the abstract. Please make sure to maintain consistency.
	Lines 10-14- the word meta analyses has to be mentioned in abstract and title as well
	Lines 42-43- what about east Africa, west Africa- are they excluded? If so, that needs to be stated
	Line 54- What kind of unpublished studies will be considered? News paper clibs, web pages etc. need to be clearly stated
	Page 7
	Line 6- Not a good exclusion criteria. Very rarely studies get published in more than one journal
	Line 13- If you exclude these groups, you are also missing out on the high risk population, therefore needs justification

	General comment- Need to be clear if we are excluding treatment of LTBI in this review
	Page 8
	Line 49-51- Attributes from the STROBE statement would be more appropriate for the quality score
	Page 11
	Line 22- 25- Secondary outcomes need to be clear and concise for eg will you include LTBI treatment?

REVIEWER	Robert J Wilkinson Imperial College London, UK
REVIEW RETURNED	03-Jul-2016

GENERAL COMMENTS	A proposal to conduct a systematic review to assess the prevalence of tuberculin skin test positivity in African populations is presented. I am not aware such an analysis has been conducted before and the results might indeed be of interest generally and to health planners. There are some points the authors may wish to consider 1. Greater emphasis should be placed on the age of participants in whatever studies are found as the prevalence of sensitisation tends to increase with age. 2. I was unsure why ascertainment of sensitisation by IGRA had been excluded. As the authors point out the test has little greater predictive ability over the TST in Africa but many studies document disconcordance with the TST results. I think it would be of interest to include such studies as it is generally agreed IGRA is also a measure of sensitisation 3. the major confounder of results will be HIV-1 status and insufficient detail of how this variable will be handled (and whether it was ascertained in studies) is provided. 4. There are several instances of incorrect preposition use 5. When the abstract discusses odds ratios what odds ratios is it intended to calculate? 6. reference 21 is a very obscure reference for the point being made 7. Page 6 what does 'TST confirmed tuberculosis antigens' mean? 8. Why exclude special at risk groups? Again this might be an interesting sub analysis to be presented either completely separately or in a separate table. These groups are actually the highest priority for treatment so their exclusion limits the translational potential of the review

	9. Watch use of italics for species names

VERSION 1 – AUTHOR RESPONSE

Page 2
Line 13- What is the strategy to address studies which have calculated LTBI using both TST and IGRA?
Response: We will use and report both TST and IGRA calculated LTBI prevalence

Line 20- 'Any study design' is too vague, need to be clearer on what type of studies will be included
Response: The sentence was corrected, now reads cross-sectional, "cohort and case control studies will be included".

Page 3
Line 5- Here you mention summarise the burden? But the extract states 'to evaluate the burden'. I think the study research question needs to be very clear
Response: "summarise" was deleted and replaced with "to evaluate the burden and risk factors of LTBI in Africa."

Line 19-26- Not clear what the author wants to state and how is this is a strength and limitation of the study
Response: The strength and/limitation in line 19-26 was deleted

Page 4
Line 10-12- The study referenced Corbett et al only states an estimated 30% of the world population (1.8 billion people) carried MTB in 2000. Please correct this statement
Response: Sentence was corrected now reads "Modelling carried over a decade ago reports that an estimated 30% of the world population (1.8 billion people) carried LTBI in 2000"

Line 26-28- Latent TB infection estimates increasing with immunosuppression- If TST has been used in these studies, it is wise to address the limitation of the test in anergic and immunosuppressive population.
Response: The point was addressed and studies with IGRA confirmed LTBI were included

Line 28-30- This doesn't fit well here. Maybe you can move this to the first few lines
Response: The sentence was moved to introduction: "Tuberculosis is the second leading cause of mortality from an infectious disease globally after the human immunodeficiency virus (HIV) [5]. In 2013, the World Health Organization (WHO) estimated 9 million new TB cases and 1.5 million tuberculosis deaths globally, of which 80% of the cases and 70% of deaths were reported in low and middle income countries."

Lines 40-49- Other risk factors like Age, diabetes, malnutrition etc. should also be mentioned.
Response: Other risk factors of LTBI such as age, diabetes, and malnutrition added.
Page 5
Lines 3-5- How can we screen 1/3 of the world and treat them for LTBI? This statement is very loose, broad with no evidence base and I suggest removing this.
Response: The following sentence has been removed: "Addressing the growing burden of tuberculosis in Africa and the rest of the world requires that individuals are screened and treated for LTBI."

Page 6
Lines 3-5 The previous page talks about the lack of good tools for latent TB diagnoses and the

research question doesn't gel with the previous section. The case for doing this review is different to what was stated in the abstract. Please make sure to maintain consistency.
Response: Objectives and research question were aligned to what's stated in the abstract

Lines 10-14- the word meta analyses has to be mentioned in abstract and title as well
Response: This was corrected "and a meta-analysis" added to title and in introduction section of the abstract

Lines 42-43- what about east Africa, west Africa- are they excluded? If so, that needs to be stated
Response: They are part of sub-Saharan Africa

Line 54- What kind of unpublished studies will be considered? Newspaper clips, web pages etc. need to be clearly stated
Response: This was corrected, now indicates "thesis, bulletins, reports and conference proceedings"

Page 7
Line 6- Not a good exclusion criterion. Very rarely studies get published in more than one journal
Response: Sentence on duplicate publications was deleted

Line 13- If you exclude these groups, you are also missing out on the high risk population, therefore needs justification
Response: This was deleted: "Studies confined to subgroups of people with LTBI (e.g. healthcare workers or miners)". This population group will now be included in the analysis to additionally assist in identifying population with greatest burden and to determine trends in this high risk population group in different regions of Africa.

General comment- Need to be clear if we are excluding treatment of LTBI in this review
Response: We will not be including LTBI treatment

Page 8
Line 49-51- Attributes from the STROBE statement would be more appropriate for the quality score
Response: This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta- Analyses Protocols (PRISMA-P) 2015 Statement

Page 11
Line 22- 25- Secondary outcomes need to be clear and concise for eg will you include LTBI treatment?
Response: We will not be including LTBI treatment. We will assess factors associated with LTBI

VERSION 2 – REVIEW

REVIEWER	Neil Schluger Columbia University
REVIEW RETURNED	06-Sep-2016

GENERAL COMMENTS	I have no further comments. I think the authors have responded satisfactorily to prior comments.

REVIEWER	Padmanesan Narasimhan Lecturer, School of Public Health and Community Medicine, The University of New South Wales, Sydney, Australia, NSW 2052

| **REVIEW RETURNED** | 21-Sep-2016 |

| **GENERAL COMMENTS** | All my comments have been addressed in this paper |